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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,743	FLYGARE ET AL.	
	Examiner	Art Unit	
	Deepak R. Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,11,18,36,41,43,44,54-62,89 and 95-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,36,43,44,54-62,89,96,97,99 and 101* is/are rejected.

7)☒ Claim(s) *3,11,18,41,95,98 and 100* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *060104 & 091503*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on June 1, 2004.

Claims 1-3, 11, 18, 36, 41, 43-44, 54-62, 89 and 95-101 are pending in this application.

The rejections of the previous office action are rendered moot by the amendments.

The following rejections are under new grounds:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-44, 54-60, 96-97, 99 and 101 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a disease state characterized by abnormally high levels of low density lipoprotein particles or cholesterol in the blood, does not reasonably provide enablement for **preventing** the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the

claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The scope of the claims is not adequately enabled solely based on the ability of the compounds to increase LDL receptor expression in Hep G2 cells, provided in the specification. First, the instant claims cover disorders that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Further, the claims are drawn to not only treatment but also **prevention** and there is no disclosure regarding how the diseases are prevented. The specification provides that the therapeutic use of compounds will be to directly or indirectly upregulate LDL receptor synthesis (see page 4). The only specific disease provided in the specification is atherosclerosis. High levels of LDLs are associated with atherosclerosis and HDLs help to remove cholesterol from the blood. In humans, the development of atherosclerosis is positively and inversely correlated with the plasma levels of low density lipoproteins (LDL) and high density lipoproteins (HDL) respectively. Therefore, elevated HDL levels and lower LDL levels are preferred in a therapeutic approach for atherosclerosis.

'Coronary artery diseases' are generally due to subintimal deposition of atheromas in the large and medium-sized arteries serving the heart and the complications include angina pectoris, unstable angina, cardiac arrhythmias, myocardial infarction, etc. and the specification does not provide any nexus between the disclosed activity and all the diseases encompassed by the instant claims, especially those of the coronary artery.

Test procedure and assays are provided in the specification in Example 72 and EC_{max} values for some of the compounds of the invention are provided, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to not only the treatment, but also

prevention of the various diseases embraced by the instant claims. The disorders encompassed by the instant claims include e.g., coronary artery diseases, some of which have been proven to be extremely difficult to treat, as the precise pathogenesis of all of the coronary artery diseases is unknown or unclear. There are multitude of risk factors contributing to various coronary artery diseases. The treatment for a specific coronary heart disease varies depending on the symptoms and how much the disease has progressed. Not one compound -- let alone a genus of thousands of compounds, could possibly be effective against all types of coronary heart diseases generally.

Further, there is no reasonable basis for assuming that the compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent (based on the definitions of R^1 and R^2) and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

The scope of the above method claims is not adequately enabled solely based on proton pump inhibitory activity provided in the specification. The instant claims are drawn to 'a method of treating or **preventing** a disease....' and therefore, the instant claim language embraces disorders not only for the treatment, but also for 'prevention', which is not remotely enabled. The instant compounds are disclosed have the ability to increase LDL receptor expression and it is recited that the instant compounds are useful in the 'prevention' of various diseases for which applicants provide no competent evidence. 'To prevent' actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the 'prevention' effect. The

only test data in the specification provides assay measuring the activity of the compounds, however, it is inconceivable as to how the claimed composition, not only treat but also 'prevent' a myriad of diseases embraced by the instant claims. Further, there is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

The breadth of the claims

The breadth of the instant claims are seen to encompass methods for treating or preventing disease state characterized by abnormally high levels of LDL, e.g., atherosclerosis.

The nature of the invention

Currently, there are no known agents with the chemotherapeutic efficacy to **prevent** all types of arterial diseases. The art does not disclose an active agent or combination of active agents, which is recognized to prevent the conditions cited supra. The prior art does not teach or disclose a treatment modality wherein healthy subjects are administered an active agent or agent(s) and there is evidence that none of the associated symptoms or disease state characteristics are ever manifested. The disclosure does not direct the skilled artisan to art, which satisfies the requirement for **preventing** a disease state associated with low density lipoprotein particles or cholesterol in blood.

The state of the prior art

A search based on some of the diseases recited in the claims revealed the following statements that establishes there are no known agents or drugs that are administered in preventing these disorders, some of the relevant segments of information are provided here. The Merck Manual (Seventeenth Edition) provides that "The fate of LDL is unclear". "Precisely what causes atherosclerosis is not known", see http://www.lef.org/protocols/prtcl-015.shtml. There was no conclusive evidence for the prevention of any of the claimed diseases.

The level of one of ordinary skill

The level of skill is that of a MD or PhD.

The level of predictability in the art

Since the art does not disclose any chemotherapeutic preventive agents, the skilled artisan would not predict, in the absence of proof to the contrary, that the active agent(s) instantly claimed are efficacious in preventing the claimed diseases. The assertion of a broad application as set forth in the instant method claims necessarily requires evidence to support applicant's asserted methods. The examiner notes there are no known pharmaceutical agents recognized as **preventive** agents for the conditions claimed, and one of skill in this art could not predict, from the evidence of record, that the active agents asserted to be useful in the instantly claimed method, can indeed prevent atherosclerosis, pancreatitis, etc.

The amount of direction provided by the inventor

The examiner notes, there is not seen sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or references to same in the prior art to provide the skilled artisan with sufficient guidance to practice the instant preventive

method. **Prevention** is seen to encompass administering the active agent to a baby or small child or healthy adult, and noting the fact that, symptoms of the disease states such as atherosclerosis, etc. never manifest themselves. The data and evidence provided in the instant disclosure leads the examiner to doubt the objective truth of assertions of prevention of the disorders of the claims.

The existence of working examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). There is not seen in the disclosure, sufficient evidence to support applicant's claims of prevention. There is not seen sufficient working examples or data from references of the prior art providing a nexus between that which applicant asserts as proof of **a method for preventing** diseases due to abnormally high levels of low density lipoprotein particles or cholesterol in blood; or extrapolation from the data and evidence currently provided on the record to support methods drawn to **preventing** any condition.

The quantity of experimentation needed to make or use the invention

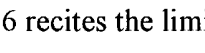
The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment or prevention. The disclosure does not provide any guidance towards the dosage regimen required

to facilitate the prevention of the claimed disorders, nor indicate competent technical references in the appropriate method of preventing.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 36 recites the limitation "that $-NR^1R^2$ is the cyclic group  " in lines 1-2. There is insufficient antecedent basis for this limitation in claim 2 on which claim 36 is dependent. Claim 2 recites that 'R^2 is optionally substituted heteroaryl' and therefore, does not include the cyclic group formed by N, R^1, R^2 and E together.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 61 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Ishii et al., CAPLUS Abstract 108:177077 (1988). The instantly claimed compounds read on reference disclosed compound (RN 113840-92-9), see the enclosed copy of the CAPLUS search report.
2. Claims 61 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Nazareth et al., CAPLUS Abstract 102:109290 (1985). The instantly claimed compounds read on reference disclosed compound (RN 94720-26-0), see the enclosed copy of the CAPLUS search report.
3. Claims 1, 2, 36, 43, 44, 58, 59, 61, 62, 89 and 97 are rejected under 35 U.S.C. 102(b) as being anticipated by Iwata et al., CAPLUS Abstract 116:214490 (1992). The instantly claimed compounds read on reference disclosed compound (RN 140893-46-5), see the enclosed copy of the CAPLUS search report.
4. Claims 61 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Posner et al., CAPLUS Abstract 107:23211 (1987). The instantly claimed compounds read on reference disclosed compound (RN 107383-86-8 or 107438-90-4), see the enclosed copy of the CAPLUS search report.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saupe et al., U.S. Patent No. 4,881,969 (cited in IDS). The reference teaches arylsulfonamidonaphthyridine compounds, see formula I in col. 1, and species of 1.119 and 1.123 in Table 1a. The reference compounds are taught to be useful as herbicidal agents, see the abstract. The instant claims exclude the reference disclosed compounds (see the proviso), however, include compounds wherein either R^1 is methyl or R^2 is further substituted by a methyl. Therefore, the instantly claimed compounds differ from the reference compounds by a $-CH_2$ group and it is well established that compounds that differ by a $-CH_2$ group are structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are *prima*

facie obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

Allowable Subject Matter

Claims 3, 11, 18, 41, 95, 98 and 100 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Receipt is acknowledged of the Information Disclosure Statement filed on June 1, 2004 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

September 7, 2004